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EXAMINER	
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ART UNIT	PAPER NUMBER
1649	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/992,994	RASO, VICTOR	
	Examiner	Art Unit	
	STACEY MACFARLANE	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85 and 86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 12, 2009 has been entered.

Response to Amendment

2. Claims 85 and 86 have been amended as requested in the amendment filed on January 12, 2009. Following the amendment, claims 85 and 86 are pending in the instant application and are under examination in the instant office action.

3. Applicant's arguments filed on January 12, 2009 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 85 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Claim recites “physiological levels” of albumin,

however, the specification does not clearly define what concentration range is considered to be physiological.

On pages 4-5 of Remarks filed January 12, 2009 Applicant traverses the rejection on the grounds that Applicant has provided a publication demonstrating the physiological level of human albumin as known in the art and argues that "unless Examiner can provide a showing that the physiological level of albumin changed ...the reference is more than adequate to support Applicant's claim of the physiological concentration of albumin in a human". While this has been considered in full it is not found persuasive for the following reasons.

In *Halliburton Energy Services, Inc. v. M-I LLC*, 514 F.3d 1244, 1255, 85 USPQ2d 1663 (Fed. Cir. 2008) the court stated,

> We [the CAFC] note that the patent drafter is in the best position to resolve the ambiguity in the patent claims, and it is highly desirable that patent examiners demand that applicants do so in appropriate circumstances so that the patent can be amended during prosecution rather than attempting to resolve the ambiguity in litigation."

The CAFC noted that claims were held indefinite in circumstances where a claim includes a numeric limitation without disclosing which of the multiple methods of measuring that number should be used. Such is the case here, where Applicant's claims recite "physiological levels of human serum albumin" and within the art there is discrepancy as to the levels measured. There is no disclosure within the instant specification as to what levels known in the art are encompassed by the term "physiological levels of human serum albumin", and therefore one of ordinary skill in the art would not be reasonable apprised as to the scope of ranges of concentrations that

should be used in the method. Examiner submits the following references which demonstrate that physiological levels of human serum albumin vary both with age and with respect to whether one is ambulatory state (Bennington J.L. in: Saunders Dictionary and Encyclopedia of Laboratory Medicine and Technology, Philadelphia, W.B. Saunders Co., 1987, p.1647; Rush University Medical Center, Normal Ranges for Common Laboratory Tests [online] retrieved on 2009-03-11, from URL:http://www.rush.edu/webapps/rml/RMLRangesCMP.jsp). Specifically, normal range for adults is 35-50 g/L, for adults over 60 years of age 34-48 g/L, on average 0.3 g/L higher in ambulatory individuals, and the range is broader in pediatric populations less than 3 years old, 25-55 g/L. Applicant has not explicitly defined "physiological levels" within the specification. When a numerical limitation within the claims, such as "physiological level", can be interpreted by one of ordinary skill in the art as spanning different ranges of concentrations, then the meaning of that recitation is indefinite. The claim is further unclear in that claim 86 replaces the recitation of "physiological levels" with "up to 60 mg/ml" encompassing levels of 0 g/L or 60 g/L, which are well outside the normal physiological ranges known in the art. Therefore, the claim is rejected as being indefinite.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. As currently amended, Claims 85 and 86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vivo* method of forming an immune complex comprising contacting beta-amyloid with an antibody that specifically binds in the presence of physiological levels or up to 60 mg/ml of human serum albumin and subsequent *in vitro* detection of the immune complex in the presence of 60 mg/ml human serum albumin (Table 3 and pg. 26 lines 7-11); the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims, drawn to a method of forming an immune complex comprising any antibody against any beta-amyloid epitope in the presence of physiological levels of human serum albumin.

On pages 5-6 of Remarks filed, Applicant traverses the rejection on the grounds that the specification is fully enabled for detection methods as performed in vivo, but nonetheless has amended the claims to recite step d) and states, "these amendments essentially make the last step of Claims 85 to 86 in vitro steps ...Therefore, Applicant submits that the specification as filed provides support for the pending claims" (page 6). While these arguments have been fully considered they are not persuasive to overcome a rejection of the claims based upon lack of enabling support for the full scope of the claims for the following reasons.

The scope of the method remains too broad. The broadest reasonable interpretation of the claimed method is that it provides for formation of an immune complex comprising *any* beta-amyloid protein, *any* epitope within said protein and *any*

anti-beta amyloid antibody in the presence of physiological levels or up to 60 mg/ml human serum albumin. As opposed to the claims, what is disclosed about the claimed method is narrow: The invention is based upon the finding that one specific anti-Aβ monoclonal antibody ("5A11") binds to ^{125}I-Aβ_{1-40} in the presence of human serum albumin (HSA) at 60 mg/ml (Table 3 and pg. 26 lines 7-11). This is the sole working example. Therefore, there is insufficient guidance as to how to perform the method with any antibody and any epitope in the presence of physiological levels or up to 60 mg/ml of human serum albumin with a reasonable expectation of success. Absent such specific guidance in the disclosure, one of ordinary skill in the art would rely upon the state of the art at the time of filing with respect to beta-amyloid-antibody immune complex formation in the presence of albumin.

The state of the art prior to filing established that human albumin binds to specific epitopes within beta-amyloid or full-length APP and displays a differential effect on the masking of antibody binding to amyloid beta antigens. The following prior art states, "the unique feature of human albumin in association with natural β-amyloid-containing proteins, including full-length APP, seems to be its masking activity for epitope(s) in β-amyloid by binding ... Furthermore, it seems that the discrepancy in masking effect between the β-amyloid 8/17 epitope(s) and cytoplasmic domain epitope(s) in APP results from the specificity of the binding site(s) of albumin for natural APP" (page 3301, Matsumoto et al., NeuroReport, 8:3397-3301, 1997). Therefore, this reference indicates that at the time of filing, unpredictability remained within the art with respect to the formation of beta-amyloid-antibody immune complexes in the presence of physiological

levels of human serum albumin. Specifically, the prior art teaches that the formation of an immune complex is highly dependent upon the specific epitope site, the ability of albumin to mask that specific site, and the binding affinity of the antibody in the presence of albumin.

The standard of an enabling disclosure is not the ability to make and test if the invention works but one of the ability to make and use with a reasonable expectation of success. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of Genentech, Inc, v. Novo Nordisk, 42 USPQ 2d 1001, (CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one cannot follow the guidance presented therein, nor the guidance known in the art at the time of filing, and practice the claimed method to the full scope of the claims for the formation of any immune complex between beta-amyloid and antibody, without first making a substantial inventive contribution. Therefore, Claims 85 and 86 are rejected under 35 U.S.C. 112, first paragraph, for failing to meet the enablement requirement.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. As currently amended, Claim 86 is rejected under 35 U.S.C. 102(b) as being anticipated by Terryberry et al. (1998) as cited in the Office Action mailed 9/10/2008.

Applicant is reminded that in order to be fully responsive, a response to an Office Action must address every ground of rejection. MPEP 714.02. There is no traverse of the rejection of claims as being anticipated by Terryberry et al. in the Remarks filed 1/12/2009.

Claim 86 is drawn to a method for forming an immune complex comprising (a) providing beta-amyloid in the presence of up to 60mg/ml human serum albumin; (b) forming an incubation mixture comprising the components of step a) and an antibody specific for a beta-amyloid epitope; (c) incubating the mixture of step b) under conditions appropriate for the binding of antibody to antigen to form an incubation mixture; and (d) removing a sample from the incubation mixture of step c) and detecting the immune complex of beta-amyloid and antibody in the presence of up to 60 mg/ml of human serum albumin.

The Terryberry et al. reference teaches detection of autoantibodies against beta-amyloid peptide 1-42 (βAP_{1-42}) and detection of the antibody-antigen complex using EIA and patient serum comprising up to 60 mg/ml of albumin. Specifically microtiter plates

were coated with the βAP_{1-42} antigen and patient serum samples were reacted with the antigen at a dilution of 1:300 (page 206 last paragraph). In the reference the first 3 steps of the method occur in the patient in vivo, where beta-amyloid is in the presence of physiological levels of albumin or up to 60mg/ml of human serum albumin and autoantibodies are present under conditions appropriate for the binding of antibody to antigen. The method then teaches removal of a serum sample from the patient and detection of the antibody–antigen immune complex in patient sera diluted 1:300. The reference does not specifically disclose the ages of the patients but, even at a dilution of 1:300, the level of serum albumin in the samples would anticipate the "up to 60mg/ml" of the claims, since this limitation encompasses values of 0 to 60 mg/ml. Therefore, the method of the instant claim fails to distinguish over that of the prior art.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claim 85 is rejected under 35 U.S.C. 103(a) as being unpatentable over Terryberry et al. (1998) as applied to claim 85 above, and further in view of Matsumoto et al., NeuroReport, 8:3397-3301, 1997.

Claim 85 is drawn to a method for forming an immune complex comprising (a) providing beta-amyloid in the presence of physiological levels of human serum albumin; (b) forming an incubation mixture comprising the components of step a) and an antibody specific for a beta-amyloid epitope; (c) incubating the mixture of step b) under conditions appropriate for the binding of antibody to antigen to form an incubation mixture; and (d) removing a sample from the incubation mixture of step c) and detecting the immune complex of beta-amyloid and antibody in the presence of physiological levels of human serum albumin.

The Terryberry et al. reference teaches a method of forming an immune complex between autoantibodies specific for beta amyloid, comprising detection of the βAP_{1-42} epitope-autoantibody complexes in patient sera diluted 1:300. Sera at this dilution would consist of albumin at levels "up to 60mg/ml", as required by claim 86.

Since the Terryberry et al. dilute the sera samples, they do not teach detection of the antigen-antibody complex "in the presence of physiological levels of human serum albumin". The Matsumoto et al. reference, however, teaches that it was well-known within the art prior to filing that "the unique feature of human albumin in association with natural β-amyloid-containing proteins, including full-length APP, seems to be its masking activity for epitope(s) in β-amyloid by binding ... Furthermore, it seems that the

discrepancy in masking effect between the β-amyloid 8/17 epitope(s) and cytoplasmic domain epitope(s) in APP results from the specificity of the binding site(s) of albumin for natural APP ...Albumin is, therefore, one of the indispensable components to understand the pathophysiology of β-amyloid deposition *in vivo*" (page 3301 and Figure 3).

It would have been obvious for one of ordinary skill in the art to perform the method for forming immune complexes between a beta-amyloid epitope and an antibody that binds said epitope, as taught by Terryberry et al., in the presence of "physiological levels" of human serum albumin, as taught by Matsumoto et al. A skilled artisan would be motivated to combine because the Matsumoto explicitly teaches human albumin as a protein that binds specific epitopes of beta-amyloid and APP and serves to mask antibody binding. Therefore, if one of ordinary skill would want to assess the in vivo binding affinity of an antibody to a beta-amyloid epitope, one would easily recognize that said binding would have to be assessed in the presence of physiological levels of human albumin. Therefore, the invention as a whole is *prima facie obvious*, if not actually anticipated by the reference.

Conclusion

13. No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is

(571)270-3057. The examiner can normally be reached on M-W and ALT F 5:30 to 3:30, TELEWORK-Thursdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
Examiner
Art Unit 1649

/John D. Ulm/
Primary Examiner, Art Unit 1649